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Should strict normoglycaemia be maintained in critically ill children?

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Sir: Several recent studies clearly identify the development of hyperglycaemia as an important risk factor in terms of mortality and morbidity of critically ill patients. In patients undergoing cardiac surgery, hyperglycaemia has been associated with a substantial mortality risk and delayed extubation [1, 2]. Strong evidence favouring a strategy targeting strict glucose control (4.5–6.0 mmol/l) came from the landmark prospective, randomized, controlled study on intensive insulin therapy in adult surgical critically ill patients [3]. Recently, the clinical benefits of this therapy in adults were largely confirmed in a large, randomized, controlled trial in a strictly medical adult ICU patient population [4]; however, whether the maintenance of normoglycaemia in critically ill children is also beneficial on patient outcome is undetermined. In an effort to analyse the presently available evidence related to paediatric critically ill patients, we performed a structured critical appraisal of the literature.

In critically ill children (patient) does insulin therapy in order to maintain strict normoglycaemia (intervention) improve survival, or reduce morbidity (outcome)? We have performed the following search strategy: Secondary (Cochrane library) and primary (PubMed) sources were included in the search. These databases were searched for: ("Insulin"[Mesh] *or* "Hyperglycemia"[Mesh] *or* "Glucose Metabolism Disorders"[Mesh] *or* "Glucose"[Mesh]) *and* ("Critical Illness"[Mesh] *or* ("Intensive Care"[Mesh] or "Intensive Care Units, Pediatric"[Mesh])) *and* systematic [sb] *not* ("Diabetic Ketoacidosis"[Mesh] *or* "Diabetes Mellitus"[Mesh]). Our search yielded 37 results, five relevant to the question, two related to children. One of the publications used a pooled database [4] partly described in a previous study. [3] One study was non-observational only. The three remaining studies are given in Table 1.

In critically ill adults, it has been shown that maintenance of strict normoglycaemia (4.5–6.0 mmol/l) with intensive insulin therapy substantially prevents morbidity and reduces mortality [4]. The risk of hypoglycaemia increases with this therapy, but it is unclear whether this is truly harmful in the setting of adult intensive care. In paediatric critically ill patients, hyperglycaemia is prevalent and is associated with a worse outcome [5, 6]. This association in itself, however, does not imply a causal relation. Whereas in adult studies maintenance of blood glucose levels between 80 and 110 mg/dl (4.5–6.0 mmol/l) has shown to reduce both mortality and morbidity [4], in the described paediatric studies higher glucose levels above 150 mg/dl (8.3 mmol/l) or above 178 mg/dl (10 mmol/l) have been found to be predict mortality [5, 6]. Uniform criteria to define hyperglycaemia in critically ill children have yet to be established and may differ between age groups. Moreover, the acute phase of sepsis

Reference	Study group	Level of evidence	Outcome	Key results (95% CI)	Comments
[*4*]	Adult ICU patients, $n = 2{,}748$; conventional insulin treatment group $n = 1{,}388$; intensive insulin treatment (IIT) group $n = 1{,}360$	Meta-analysis (level 1a)	Mortality, critical illness polyneuropathy, renal failure, hypoglycaemia	Mortality: relative risk reduction (RRR) 19% (95% CI: 2–35%); absolute risk reduction (ARR): 0.03 (0.004–0.056); number needed to treat (NNT): 33 (18–281)	Study limited to adults; insulin therapy in the conventional treatment group was initiated when blood glucose levels exceeded 215 mg/dl (12 mmol/l), and adjusted to keep blood glucose between 180 and 200 mg/dl (10–11 mmol/l); in the intensive insulin treatment group, therapy was initiated when blood glucose was above 110 mg/dl (6 mmol/l) and adjusted to maintain blood glucose between 80 and 110 mg/dl (4.5–6 mmol/l)

Table 1 Overview of relevant papers

Reference	Study group	Level of evidence	Outcome	Key results (95% CI)	Comments
				New renal failure: RRR 42 (18–65), ARR 0.032 (0.014–0.050), NNT 31 (20–71)	
				Critical illness polyneuropathy: RRR 40 (25–56), ARR 0.063 (0.038–0.088), NNT 16 (11–26)	
				Hypoglycemia: RRR −528% (629 to −427%), ARR −0.095 (−0.013 to −0.077), NNH 11 (9–13)	Strict glucose control reduced in-hospital mortality for patients with > 3 ICU days but did not lead to a difference in overall in-hospital mortality
				Mortality or neurological sequelae in hypoglycaemic patients: RRR 50% (−237 to 100%), ARR −0.001 (−0.005 to 0.003), NNH 1,000 (211 to infinite)	
[*6*]	Pediatric septic shock patients ($n = 57$)	Single-center, prospective observational cohort study (level 2c)	Mortality	Peak glucose level in non-survivors 262 ± 110 mg/dl (14.5 ± 6 mmol/l) was higher than in survivors: 167.8 ± 55 mg/dl (9.5 ± 3 mmol/l; $p < 0.01$)	Observational pediatric study; univariate analysis identified three possible factors that could be associated with increased mortality (higher glucose level, male gender, pediatric risk of mortality score II above 10); multivariate analysis demonstrated that peak glucose level was the only independent risk factor associated with mortality
				Best peak glucose level predicting death was 178 mg/dl (10 mmol/l), sensitivity 0.71, specificity 0.72, relative risk of death in hyperglycaemic patients 2.59 (1.37–4.88)	Severity of illness was not reported; 941 of 1,927 patients excluded because of absence of glucose measurement, leading to a possible selection bias
[*5*]	Pediatric critically ill, non-diabetic patients ($n = 942$)	Single-center, retrospective observational cohort study (level 2c)	Mortality and length of stay	Peak glucose level above 150 mg/dl (8.3 mmol/l) within 10 days of initial glucose measurement predicted death with a sensitivity of 81% (68–93%), specificity 51% (48–54%), relative risk of death 4.13 (1.83–9.32); length of stay in hyperglycaemic group was higher 6.1 ± 9.6 vs. 4.0 ± 6.0 days ($p = 0.001$)	

Table 1 Continued

in children may differ significantly from the hyperinsulinaemic hyperglycaemia associated with insulin resistance in adult sepsis. In a recent study it has been shown that children in shock due to meningococcal sepsis showed signs of insufficient insulin response to hyperglycaemia, whereas patients without signs of shock were insulin resistant [7]. In paediatric critically ill patients, hypoglycaemia is also prevalent and is related to increased mortality [8]. Hypoglycaemia was significantly more common in patients receiving intensive insulin therapy [4]. Insulin therapy in sick children with high blood glucose levels, exceeding 178 mg/dl (10 mmol/l), can be advocated, but based on current evidence, there is insufficient data to extrapolate to critically ill children that strict glucose control is beneficial. Currently, two large registered and ongoing European randomised controlled trials on the subject of tight glucose control in critically ill paediatric patients are being performed: Control of Hyperglycaemia in Paediatric Intensive Care (ISRCTN 61735247, London, http://www.chip-trial.org.uk) and Tight Glycemic Control With Intensive Insulin Treatment in PICU (NCT00214916, Leuven).

In conclusion, no randomised controlled studies focusing on strict glucose control in paediatric patients were found. In critically ill adults maintenance of strict normoglycaemia with intensive insulin therapy reduces morbidity and mortality (evidence grade A). In paediatric ill patients, hyperglycaemia is prevalent and levels above 178 mg/dl (10 mmol/l) are associated with increased mortality (grade B).Ill children, however, are also susceptible to hypoglycaemia. Based on current evidence, insulin therapy aimed at strict glucose control [blood glucose levels between 80 and 110 mg/dl (4.5–6 mmol/l)] cannot be recommended in paediatric critically ill patients. Any future change in practice should be based on evidence from current randomised clinical trials.

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